

Prevalence of Vitamin B₁₂ and folic acid deficiency in HIV-positive patients and its association with neuropsychiatric symptoms and immunological response

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Abstract

Background: Deficiency of micronutrients is prevalent even before the development of symptoms of HIV disease and is associated with accelerated HIV disease progression. **Aims:** This study evaluates the prevalence of folate and Vitamin B₁₂ deficiency in HIV-positive patients with or without tuberculosis (TB) and its association with neuropsychiatric symptoms and immunological response. **Settings and Design:** Cross-sectional, observational study in an outpatient setting. **Patients and Methods:** Four groups of HIV-positive patients with TB (Group I), HIV-positive patients with neuropsychiatric symptoms (Group II), HIV-positive patients without neuropsychiatric symptoms or TB (Group III), and HIV-negative controls with neuropsychiatric symptoms (Group IV). Vitamin B₁₂ and folate estimation was done using carbonyl metallo-immunoassay method. **Statistical Analysis Used:** ANOVA, Kruskal-Wallis and Mann-Whitney, Pearson's correlation. **Results:** The prevalence of folic acid deficiency was 27.1% in the Group I, 31.9% in the Group II, 23.4% in the Group III, and 32% in the Group IV being higher in patients with neuropsychiatric symptoms in both HIV and non-HIV patients. The prevalence of Vitamin B₁₂ deficiency was 18.8% in Group I, 9.1% in Group II, 4.8% in Group III, and 16.7% in Group IV. The patients with folate deficiency had more severe depression and anxiety. **Conclusion:** Nearly, 30% of the HIV patients had a folic acid deficiency, and about 10% of the HIV patients had Vitamin B₁₂ deficiency. The folate deficiency was highest among neuropsychiatric patients with or without HIV infection and Vitamin B₁₂ deficiency was higher among HIV patients with TB.

Key words: Folic acid, HIV, neuropsychiatric symptoms, Vitamin B₁₂

INTRODUCTION

Micronutrients such as Vitamins B, C, E, and trace element selenium are essential for maintaining a responsive immune system.^[1] Their deficiencies are prevalent even before the development of symptoms of HIV disease and are associated with accelerated

HIV disease progression.^[2] Multiple nutrient deficiencies occur relatively early in the course of HIV infection. They occur due to malabsorption, altered metabolism, gut infection, altered gut barrier function, chronic diarrhea, anorexia, impaired

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nutrient storage, etc.^[3] The prevalence of specific nutrient abnormalities is widespread among HIV-infected patients compared to non-HIV patients. Several observational studies have reported that a number of micronutrient deficiencies among HIV-infected individuals are associated strongly with a faster progression to disease and death^[4,5] and raise the possibility that normalization might increase the interval of symptom-free survival. HIV-positive patients appear to require an intake of these nutrients in multiples of recommended dietary allowances when compared to normal individuals.

Micronutrients such as Vitamin B₁₂ and folic acid, whose deficiencies are found in higher numbers in HIV-infected patients^[6] and their deficiencies may typically present initially with neuropsychiatric disturbances, including depression, dementia, and demyelinating myelopathy.^[7] Folate deficiency hinders DNA synthesis and cell divisions affecting the sites of rapid cell turnover such as bone marrow. Because Vitamin B₁₂ is highly conserved through enterohepatic circulation, its deficiency from malabsorption develops after 2–5 years and the deficiency from dietary inadequacy in vegetarians develops after 10–20 years.

The association between tuberculosis (TB) and malnutrition is known since a long time. Malnutrition due to TB, reduces immunity, thereby increasing the risk of latent TB developing into active disease.^[8] Low circulating concentrations of micronutrients have been reported in patients with active TB. Most patients with active TB are in a catabolic state^[9] and some show signs of vitamin and mineral deficiencies at diagnosis.^[10] TB is one of the major opportunistic infections seen in HIV-positive patients. Low CD4 cells in HIV-infected persons indicate severely depressed immunity that makes them susceptible to fresh TB or reactivation of latent infection and rapid degradation of the clinical condition.^[11] Hence, HIV patients with TB represent a more severe disease compared to asymptomatic HIV-positive patients. TB is a useful clinical indicator in the progression of HIV infection.^[12]

This study evaluates the prevalence of folate and Vitamin B₁₂ deficiency in HIV-positive patients with or without TB and its association with neuropsychiatric symptoms and immunological response. As HIV patients with TB are likely to be nutritively more poor compared to asymptomatic HIV patients, due to double chronic inflammatory state, poor appetite, and catabolic state, they were chosen as separate groups. Comparison among patients with different levels of severity of the

disease/comorbidity in a cross-sectional study helps us to evaluate the possible relationship of deficiency of B₁₂ and folic acid deficiency with the disease severity, as well as the risk of opportunistic infection like TB.

PATIENTS AND METHODS

The present cross-sectional study is done at a tertiary care hospital in South India which has a database of nearly 2000 HIV-positive patients. The study was approved by the Institutional Ethics Committee and the patients were included in the study after their written informed consent. The study included four groups, each group consisting of fifty patients.

- Group I: HIV-positive patients with coexistent tuberculous infection
- Group II: HIV-positive patients with neuropsychiatric symptoms
- Group III: HIV-positive patients without neuropsychiatric symptoms or TB
- Group IV: HIV-negative controls with neuropsychiatric symptoms.

Neurological manifestations included stroke, central nervous system (CNS) toxoplasmosis, cryptococcal meningitis, cytomegalovirus encephalitis, and peripheral neuropathy. Psychiatric manifestations included delirium, schizophrenia, acute confusional state, dementia, depression, and severe anxiety and mood disturbances.

Definition of HIV positivity was taken as any patient tested positive by two HIV enzyme-linked immunosorbent assay tests and a mono spot test using three different antigens (or) three mono spot test positive using three different antigens by voluntary counseling and testing center established by the National AIDS Control Organization, India.

Confirmation of coexistent tubercular infection as evidenced by sputum positivity/radiological evidence/tissue diagnosis of extrapulmonary TB by fine-needle aspiration cytology (FNAC)/molecular diagnosis of extrapulmonary TB by polymerase chain reaction (PCR) positivity for tubercular antigen in cerebrospinal fluid (CSF), pleural, pericardial or ascitic fluid/mantoux positive >5 mm and having a CD4 count <200 with clinical symptoms suggestive of TB.

A detailed history, including the diet history, was taken and clinical examination performed which included a detailed neurological assessment, as well as psychiatric assessment using Folstein's

Mini-Mental State Examination (MMSE) score, Hamilton Depression Scale (HAM-D), and Hamilton Anxiety Rating Scale (HAM-A) score.

Absolute CD4 count estimation was done using flow cytometry, and its normal reference range was 380–1200 cells/ μ L.

Patients in Group I underwent chest X-ray, sputum examination for acid-fast bacilli, ultrasound examination, and lymph node FNAC/biopsy of significant lymph nodes whichever was deemed necessary for diagnosis. Patients in Group II underwent computed tomography (CT) scan head/magnetic resonance imaging (MRI), CSF analysis, PCR of CSF for TB, herpes simplex virus for CNS symptoms, and nerve conduction studies (NCVs) for evidence of peripheral neuropathy which ever was needed by the patient for an adequate diagnosis. Investigation such as chest X-ray and ultrasound examination was done even for Group III patients as a part of routine HIV care. CT/MRI and CSF studies were done for Group IV controls when indicated. NCVs were done for peripheral neuropathy patients included in the Group IV as controls. An invasive investigation such as CSF studies was done only when signs and symptoms of patients were indicative of meningitis.

Vitamin B₁₂ and folate estimation was done using carbonyl metallo-immunoassay method, and reference range that was taken for Vitamin B₁₂ was 189–883 pg/ml and for folate 2.7–34.0 ng/ml.

The sample size was calculated using OpenEpi Version 3 (Open Source Epidemiologic Statistics for Public Health. www.OpenEpi.com). Assuming that population folate deficiency is 5%, a sample size of 32 per group was calculated at a confidence level of 80% and confidence limits as 5%.

Statistical analysis

Statistical analysis was done using statistical package SPSS 11.0 version (SPSS Statistics for Windows, Version 11.0. Chicago: SPSS Inc.). All the continuous variables were expressed as mean or median. Normally distributed data were analyzed by ANOVA and nonnormally distributed data were analyzed by the Kruskal–Wallis and Mann–Whitney tests. Pearson's correlation was used to analyze the association of CD4 count with folate and Vitamin B₁₂.

RESULTS

In this study, a total of 200 patients were enrolled. The first three Groups (I, II, and III) comprised a

total of 150 HIV-positive patients with fifty patients in each group (HIV cohort). Group IV included fifty patients, who manifested with neuropsychiatric symptoms and were tested for HIV negative.

The mean age of Groups I, II, III, and IV was 36.28 ± 5.93 , 39.22 ± 9.02 , 38.57 ± 8.84 , and 46.58 ± 18.53 years respectively. The ratio of males and female participants among the four groups was 40:10, 35:15, 33:17, and 29:21, respectively. The body mass index of Groups I–IV was 17.42 ± 2.84 , 17.46 ± 2.99 , 18.82 ± 3.17 , and 22.69 ± 4.77 kg/m², respectively. The median CD4 count in the study population was 139 (58.25–330.75) cells/ μ L. The median duration of illness was 18.50 (2–54.25) months.

Group I included HIV patients with co-existent tubercular infection. Of the fifty patients enrolled, 37 had extrapulmonary TB, 11 had pulmonary TB, and two had both at presentation.

Group II included HIV-positive patients with neuropsychiatric manifestations. Of the fifty patients, 21 had peripheral neuropathy, 12 had cryptococcal meningitis, 4 had cerebral toxoplasmosis, 11 had tubercular meningitis, 17 had psychosis, and 2 had a stroke.

Group III included asymptomatic HIV patients or patients with minor opportunistic infections. Of the fifty patients enrolled, 11 had oral candidiasis and 3 had *Pneumocystis jirovecii* pneumonia at presentation, while others were asymptomatic.

Among fifty Group IV patients, ten had cerebrovascular accidents, seven had peripheral neuropathy, seven had spinal cord disease, three had meningitis, three had cerebellar disorders, three had intracranial space occupying lesions, three had dementia, two had Parkinson's disease, one had motor neuron disease, another one had muscle dystrophy. Psychiatric manifestations such as schizophrenia and mood disorders were seen in ten patients.

Figure 1 shows the folic acid levels in the study population. The serum folic acid level was available in 48 patients of Group I, 47 patients of Group II, 48 patients of Group III, and in all patients of Group IV. The median folic acid levels in Groups I–IV were 5.91 (2.9–37), 3.64 (2.12–8.17), 5.08 (3.16–9.96), and 3.85 (2.08–9.30) ng/ml, respectively. Comparison of median folic acid levels between four groups did not show any statistical significance ($P = 0.39$) although levels were lower in patients with neuropsychiatric manifestations.

The prevalence of folic acid deficiency in the Group I was 27.1%, Group II was 31.9%, Group III was 23.4%, and in the Group IV it was 32%. The prevalence of folic acid deficiency was higher in patients with neuropsychiatric symptoms in both HIV and non-HIV patients [Figure 2]. There was no statistically significant difference in the prevalence of folic acid between four groups ($\chi^2 = 2.86$, $P = 0.41$) although higher proportions of patients with neuropsychiatric manifestations irrespective of the HIV status had folate deficiency.

The serum Vitamin B₁₂ level was available in 49 patients of Group I, 49 patients of Group II, 48 patients of Group III, and in all patients of Group IV. The median serum B₁₂ levels in Groups I–IV were 380 (263.45–701.05), 555 (343–1127), 460.5 (325–698.75), and 497 (258.75–1791) pg/ml, respectively [Figure 3]. Comparison of median Vitamin B₁₂ levels between four groups showed a very small statistical significance ($P = 0.053$), with the levels being lowest in patients with TB.

The prevalence of Vitamin B₁₂ deficiency in the Group I was 18.8%, Group II was 9.1%, Group III was 4.8%, and in Group IV it was 16.7% [Figure 4]. There was no statistically significant difference in the prevalence of Vitamin B₁₂ deficiency between

four groups ($\chi^2 = 0.70$, $P = 0.87$) although relatively healthy HIV-positive patients had a very low prevalence of B₁₂ deficiency.

Thus, nearly 30% of the HIV patients had a folic acid deficiency and about 10% of the HIV patients had Vitamin B₁₂ deficiency.

There was a significant correlation between CD4 and folic acid in Group III [Table 1], ($P = 0.011$). There is no significant correlation between CD4 count and Vitamin B₁₂ level in all the three groups [Table 1].

Table 2 shows the neuropsychiatric scores in all four groups of patients. HIV patients with neuropsychiatric manifestations (Group II) were noted to have the lowest mean mini-mental score when compared to Groups I and III. The score was also found to be less in Group IV, the non-HIV patients with neuropsychiatric symptoms (24.43). The difference between Group I and Group II MMSE scores was statistically significant ($P = 0.012$), as well as Group III versus Group II ($P < 0.001$) and Group IV versus Group III ($P = 0.001$). The HIV-negative group with neuropsychiatric manifestation has higher median anxiety scores than the HIV cohort. HIV groups with neuropsychiatric symptoms and TB had more depression compared to asymptomatic HIV patients.

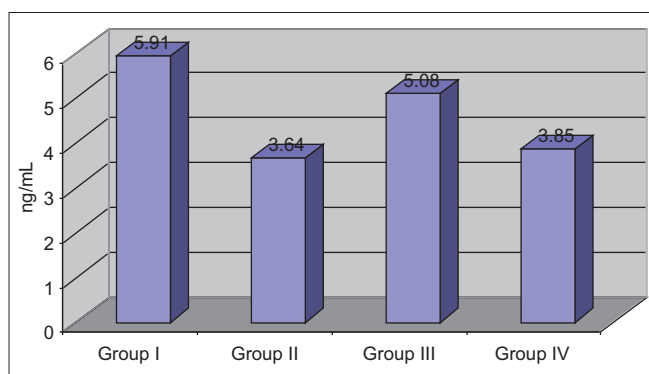


Figure 1: Serum folic acid level

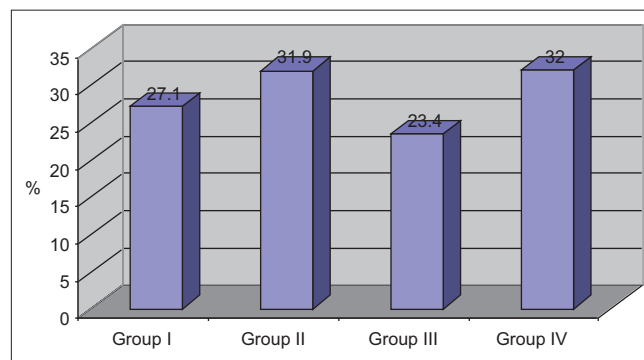


Figure 2: Prevalence of folic acid deficiency

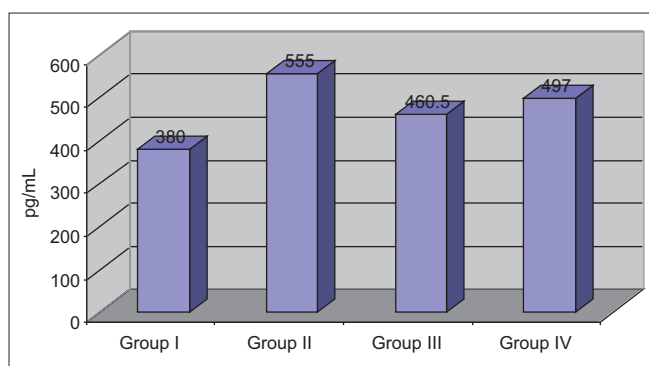


Figure 3: Serum Vitamin B₁₂ level

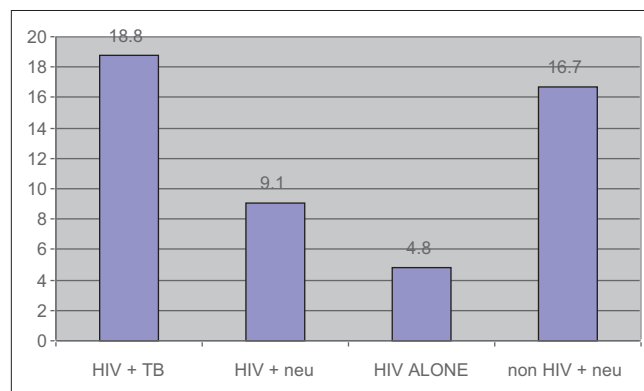


Figure 4: Prevalence of B₁₂ deficiency

Table 1: Correlation of CD4 count with folic acid and Vitamin B₁₂

Pearson's correlation	Group I		Group II		Group III	
	Folic acid	Vitamin B ₁₂	Folic acid	Vitamin B ₁₂	Folic acid	Vitamin B ₁₂
r value		0.073	0.226	-0.081	0.363	-0.111
P value	0.432	0.619	0.136	0.587	0.011	0.452

Table 2: Neuropsychiatric scores of HIV-positive cohort and HIV-negative patients

Neuropsychiatric scores	Group I	Group II	Group III	Group IV	P
Mean MMSE	26.98±2.63	24.71±4.49	27.96±2.01	24.43±4.67	<0.001
Median HAM-A	4 (3, 8)	4 (4, 8)	4 (2,6)	6 (3, 8.5)	0.195
Median HAM-D	8 (5.75, 10)	8 (6, 14)	6 (4,10)	7 (5, 10)	0.018

MMSE=Mini-mental state examinationscore; HAM-A=Hamilton Anxiety Rating Scale; HAM-D=Hamilton Depression Scale

Comparison of median scores of MMSE, anxiety, and depression scores among patients with and without folate deficiency showed significant differences with regard to anxiety and depression ($P = 0.021$, $P = 0.02$, respectively, Mann-Whitney test). There was no significant difference with regard to median MMSE score among patients with or without folate deficiency. This indicates that patient with folate deficiency had more severe depression and anxiety ($P = 0.42$).

Comparison of median scores of MMSE, anxiety, and depression scores among patients with and without Vitamin B₁₂ deficiency did not show significant differences ($P = 0.57$, $P = 0.68$, $P = 0.11$, respectively, Mann-Whitney test).

The median CD4 count in Group I was 125.5 (62.25–271.25) cells/ μ L, Group II was 89 (46.75–175.75) cells/ μ L, and Group III was 282 (132–611.75) cells/ μ L. The median baseline CD4 count was least in HIV patients with neuropsychiatric symptoms, probably indicating that progression of illness leads to significant fall in the CD4 count. Statistically significant difference in the median CD4 counts ($P < 0.001$) existed between Groups I and III and also between Groups II and III ($P < 0.001$).

DISCUSSION

The present study was aimed at determining the prevalence of folate and Vitamin B₁₂ deficiency in HIV-positive patients with or without TB and neuropsychiatric manifestations, as well as in the control group consisting of HIV-negative patients with neuropsychiatric manifestations.

Nearly, one-third of HIV-positive patients with neuropsychiatric symptoms had a folate deficiency, and nearly one-fifth of other HIV groups had folate deficiency. Controls with neuropsychiatric manifestations also had folate deficiency. The median folic acid level was lower in Group II (with

neuropsychiatric manifestations) compared to Groups I and III, as well as neuropsychiatric controls which were not significant statistically in view of the smaller sample size. This may be because of decreased dietary intake due to neuropsychiatric manifestations as well decreased absorption of folic acid due to advanced disease in Group II. The low folic acid level itself would have aggravated neuropsychiatric problems in this group as the folic acid levels in Group II can be compared to that of Group IV (HIV-negative patients with neuropsychiatric manifestations). Higher prevalence of folic acid deficiency in Groups II and IV might have played a role in diminished cognitive function and depression found in these groups. The overall prevalence of folic acid deficiency in HIV-infected individuals is nearly 25%, which is much higher than the prevalence of folic acid deficiency in the general population.

The median Vitamin B₁₂ level was lower in Group I with TB compared to other groups as the majority of neuropsychiatric problems are acute in onset, and our body has Vitamin B₁₂ storage which is adequate for around 5 years. TB being a chronic disease might have caused relatively low Vitamin B₁₂ levels in Group I. The prevalence of Vitamin B₁₂ deficiency was also highest in the Group I indicating that B₁₂ deficiency is common in chronic diseases.

Castro and Goldani in a study conducted in a small group of HIV-positive patients in Southern Brazil reported folate deficiency in 41% of patients and Vitamin B₁₂ deficiency in 6% of patients.^[6] The low serum B₁₂ level was observed in the earlier reports also.^[13] Alani *et al.* have found that folate deficiency occurs as an early event in HIV infection and that the introduction of folate prophylaxis may be justified as soon as HIV diagnosis is confirmed to delay disease progression and early occurrence of anemia.^[14] Our study showed a positive correlation between folic acid level and CD4 count. A similar association

was seen in the earlier study also.^[14] The high prevalence of Vitamin B₁₂ and folic acid deficiency in Group I indicates that special attention is required regarding micronutrient supplementation among the HIV patients who have co-existing TB and neuropsychiatric manifestations.

Mini-Mental State Examination score was lower in Group II as they had specific neuropsychiatric problems. HAM-D scores were higher in Groups I and II compared to Group III because of the advanced nature of the disease in both groups and specific CNS involvement in Group II. One more factor that might have contributed to low mini-mental score and high HAM-D score would have been the high prevalence of folic acid deficiency in this group which results in diminished cognitive function and depression. There was no significant difference between the groups with regard to HAM-A scores.

Median baseline CD4 count was less in Groups I and II compared to Group III because of the advanced HIV disease in these two groups. The incidence of opportunistic infections, mainly affecting the CNS, leading to neuropsychiatric manifestations is maximum in Group II because of low CD4 counts, and hence the lower immune status of the patients.

The median CD4 count in the study conducted by Jiamton *et al.*^[4] was 244 cells/mm³ in asymptomatic HIV-positive patients, which is comparable to the median CD4 count of found in Group III, which comprised asymptomatic HIV-positive patients. However, in a study conducted by Fawzi *et al.*^[15] in Tanzania in 1078 pregnant women with HIV infection, mean CD4 count was 429 ± 224 cells/mm³. This might have been because of early detection of HIV infection and high intake of antiretroviral treatment in this region.

Our study was limited by a small sample size and we selected specific groups of HIV-positive people with or without TB or neuropsychiatric manifestation and took only neuropsychiatric controls. The inclusion of healthy controls would have given us more accurate information on the effect of HIV infection on folic and serum B₁₂ levels.

CONCLUSION

Nearly, 30% of the HIV patients in our study had a folic acid deficiency and about 10% of the HIV patients had Vitamin B₁₂ deficiency. The folic acid deficiency was highest among neuropsychiatric patients, both with and without

HIV infection, signifying its role in causing neuropsychiatric manifestations. The prevalence of Vitamin B₁₂ deficiency was higher among HIV patients with TB. Higher prevalence of folic acid and B₁₂ deficiency in HIV patients with TB shows that more attention is required regarding micronutrient supplementation in patients with TB. CD4 count was lower in HIV patients with TB and neuropsychiatric symptoms.

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Conflicts of interest

There are no conflicts of interest.

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